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(54) Title: HUMAN TUMOR NECROSIS FACTOR DELTA AND EPSILON

(57) Abstract

The invention relates to human TNF delta and TNF epsilon polypeptides, polynucleotides encoding the polypeptides, methods for producing the polypeptides, in particular by expressing the polynucleotides, and agonists and antagonists of the polypeptides. The invention further relates to methods for utilizing such polynucleotides, polypeptides, agonists and antagonists for applications, which relate, in part, to research, diagnostic and clinical arts.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:-
  - (a) a polynucleotide sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:2;
  - (b) a polynucleotide sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:4;
  - (c) a polynucleotide sequence encoding a polypeptide comprising amino acid 39 to amino acid 233 of SEQ ID NO:2;
  - (d) a polynucleotide sequence having at least 70% identity to the polynucleotide sequence of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (e) a polynucleotide sequence comprising at least 30 contiguous bases of the polynucleotide sequence of (a), (b), (c) or (d) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (f) a polynucleotide sequence comprising at least 50 contiguous bases of the polynucleotide sequence of (a), (b), (c) or (d) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (g) a polynucleotide sequence comprising a fragment of the polynucleotide sequence of (a), (b), (c) or (d), wherein said fragment encodes a polypeptide that retains TNF-delta and/or TNF-epsilon activity;
  - (h) a polynucleotide sequence of (g) which encodes at least 30-50 amino acids of SEQ ID No's 2 or 4; and
  - (i) a polynucleotide sequence which is complementary to the polynucleotide sequence of (a), (b), (c), (d), (e), (f), (g) or (h).
2. The polynucleotide of Claim 1 wherein the polynucleotide is DNA.
3. The polynucleotide of Claim 1 wherein the polynucleotide is RNA.
4. The polynucleotide of Claim 1 wherein the polynucleotide is genomic DNA.
5. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids of SEQ ID NO:2.

6. The polynucleotide of Claim 2 which encodes a polypeptide comprising amino acid 39 to 233 of SEQ ID NO:2.
7. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids of SEQ ID NO:4.
8. The polynucleotide of Claim 2 which encodes a polypeptide comprising the amino acids 1 to 188 of SEQ ID NO:4.
9. An isolated polynucleotide comprising a polynucleotide selected from the group consisting of:-
  - (a) a polynucleotide which encodes a mature polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 97377;
  - (b) a polynucleotide which encodes a mature polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 97457;
  - (c) a polynucleotide sequence having at least 70% identity to the polynucleotide sequence of (a) or (b) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (d) a polynucleotide sequence comprising at least 30 contiguous bases of the polynucleotide of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (e) a polynucleotide sequence comprising at least 50 contiguous bases of the polynucleotide sequence of (a), (b) or (c) and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity;
  - (f) a polynucleotide comprising a fragment of the polynucleotide of (a), (b) or (c), wherein said fragment encodes a polypeptide that retains TNF-delta and/or TNF-epsilon activity;
  - (g) a polynucleotide sequence of (f) which encodes at least 30-50 amino acids of the polypeptide encoded by ATCC Deposit No's 97377 or 97457; and
  - (h) a polynucleotide which is complementary to the polynucleotide of (a), (b), (c), (d), (e), (f) or (g).

10. The polynucleotide of Claim 1 comprising from nucleotide 447 to nucleotide 1717 of SEQ ID NO:1.
11. The polynucleotide of Claim 1 comprising from nucleotide 332 to nucleotide 1717 of SEQ ID NO:1.
12. The polynucleotide of Claim 1 comprising from nucleotide 1 to nucleotide 564 of SEQ ID NO:3.
13. A vector comprising the DNA of Claim 2.
14. A host cell comprising the vector of Claim 13.
15. A process for producing a polypeptide comprising expressing from the host cell of Claim 14 the polypeptide encoded by the DNA in said vector.
16. A process for producing a cell comprising genetically engineering the cell with the vector of Claim 12 to thereby express the polypeptide encoded by the human cDNA contained in the vector.
17. A polypeptide comprising a member selected from the group consisting of:-
  - (a) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2;
  - (b) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:4;
  - (c) a polypeptide comprising amino acid residues 39 to 233 of SEQ ID NO:2;
  - (d) a polypeptide comprising amino acid residues 1 to 188 of SEQ ID NO:4;
  - (e) a polypeptide having at least a 70% identity to the polypeptide of (a), (b), (c) or (d) and having TNF-delta and/or TNF-epsilon activity;
  - (f) a polypeptide comprising at least 30 contiguous amino acid residues of the polypeptide of (a), (b), (c), (d) or (e) and having TNF-delta and/or TNF-epsilon activity.

18. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 1 to amino acid 233 of SEQ ID NO:2.
19. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 39 to amino acid 233 of SEQ ID NO:2.
20. The polypeptide of Claim 17 wherein the polypeptide comprises amino acid 1 to amino acid 188 of SEQ ID NO:4.
21. A compound which inhibits activation of the polypeptide of Claim 17.
22. A method for the treatment of a patient having need of TNF delta comprising administering to the patient a therapeutically effective amount of the polypeptide of Claim 17.
23. A method for the treatment of a patient having need of TNF epsilon comprising administering to the patient a therapeutically effective amount of the polypeptide of Claim 17.
24. A method of Claim 22 wherein said therapeutically effective amount of the polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.
25. A method of Claim 23 wherein said therapeutically effective amount of the polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.
26. A method for the treatment of a patient having need to inhibit a TNF delta polypeptide comprising administering to the patient a therapeutically effective amount of the compound of Claim 21.
27. A method for the treatment of a patient having need to inhibit a TNF epsilon polypeptide comprising administering to the patient a therapeutically effective amount of the compound of Claim 21.

28. A process for diagnosing a disease or a susceptibility to a disease related to an under-expression of the polypeptide of Claim 17 comprising determining a mutation in a nucleic acid sequence encoding said polypeptide.
29. A diagnosis process comprising analysing for the presence of the polypeptide of claim 17 in a sample derived from a host.
30. A method for identifying compounds which bind to and inhibit activation of the polypeptide of Claim 17 comprising:-  
    contacting a cell expressing on the surface thereof a receptor for the polypeptide, said receptor being associated with a second component capable of providing a detectable signal in response to the binding of a compound to said receptor, with an analytically detectable TNF delta polypeptide and a compound under conditions to permit binding to the receptor; and  
    determining whether the compound binds to and inhibits the receptor by detecting the absence of a signal generated from the interaction of the TNF delta with the receptor.
31. An isolated polynucleotide comprising a polynucleotide sequence having at least 90% identity to a member of the group (a), (b), (c), (d), (e), (f), (g) or (h) in claim 1 and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity.
32. An isolated polynucleotide comprising a polynucleotide sequence having at least 95% identity to a member of the group (a), (b), (c), (d), (e), (f), (g) or (h) in claim 1 and encoding a polypeptide having TNF-delta and/or TNF-epsilon activity.
33. An isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide with TNF-delta and/or TNF-epsilon activity and which hybridises to the complement of the polynucleotide set forth in SEQ ID NO:1 wherein said hybridisation occurs under conditions comprising hybridisation in a buffer consisting of 7% SDS, 0.5 M NaPO<sub>4</sub> pH 7.4 at 65°C and wash in a solution consisting of 0.5 x SSC, 0.1% SDS at 60°C.
34. An isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide with TNF-delta and/or TNF-epsilon activity and which hybridises to

the complement of the polynucleotide set forth in SEQ ID NO:3 wherein said hybridisation occurs under conditions comprising hybridisation in a buffer consisting of 7% SDS, 0.5 M NaPO<sub>4</sub> pH 7.4 at 65°C and wash in a solution consisting of 0.5 x SSC, 0.1% SDS at 60°C.

35. The isolated polypeptide of Claim 17 wherein said polypeptide comprises an amino acid sequence having at least 90% identity to a member of said group (a), (b), (c), (d), (e) or (f) and retains TNF-delta and/or TNF-epsilon activity.
36. The isolated polypeptide of Claim 17 wherein said polypeptide comprises an amino acid sequence having at least 95% identity to a member of said group (a), (b), (c), (d), (e) or (f) and retains TNF-delta and/or TNF-epsilon activity.
37. An isolated polynucleotide according to any one of Claims 1 to 12 or a vector according to Claim 13 or a host cell according to Claim 14 or a process according to Claims 15 or 16 or a polypeptide according to any one of Claims 17 to 20 or a compound according to Claim 21 or a method according to any one of Claims 22 to 30 or a polynucleotide according to any one of Claims 31 to 34 or a polypeptide according to Claim 35 or 36 substantially as hereinbefore described with reference to the Figures and/or Examples.

**AUSTRALIA**

*Patents Act 1990*

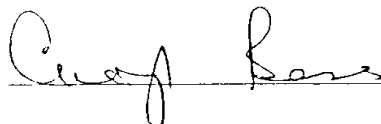
**IN THE MATTER OF** Australian Patent  
Application Serial No. 696764 by Human  
Genome Sciences, Inc.

-and-

**IN THE MATTER OF** Opposition thereto by  
Ludwig Institute for Cancer Research

THIS IS Exhibit PAWR-3  
referred to in the Statutory Declaration  
of Peter Adrian Walton Rogers  
made before me

DATED this 12<sup>th</sup> Day of November, 2001

A handwritten signature in cursive script, appearing to read "Craig Bone", written over a horizontal line.

(Signature of Witness)

Medical Practitioner



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Tumor necrosis factor-gamma

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<p>(21) International Application Number: PCT/US94/12880 (22) International Filing Date: 7 November 1994 (07.11.94)</p> <p>(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850-3338 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): YU, Guo-Liang [CN/US]; 13524 Straw Bale Lane, Darnestown, MD 20878 (US). NI, Jian [CN/US]; Apartment 204, 305 Westside Drive, Gaithersburg, MD 20878 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US).</p> <p>(74) Agents: OLSTEIN, Elliot, M. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart &amp; Olstein, 6 Becker Farm Road, Roseland, NJ 07068 (US).</p>		<p>(81) Designated States: AU, CA, CN, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>
<p>(54) Title: TUMOR NECROSIS FACTOR-GAMMA</p> <p>(57) Abstract</p> <p>A human TNF-gamma polypeptide and DNA (RNA) encoding such polypeptide and a procedure for producing such polypeptide by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptide to inhibit cellular growth, for example in a tumor or cancer, for facilitating wound-healing, to provide resistance against infection, induce inflammatory activities, and stimulating the growth of certain cell types to treat diseases, for example restenosis. Also disclosed are diagnostic methods for detecting a mutation in the TNF-gamma nucleic acid sequence or an overexpression of the TNF-gamma polypeptide. Antagonists against such polypeptides and their use as a therapeutic to treat cachexia, septic shock, cerebral malaria, inflammation, arthritis and graft-rejection are also disclosed.</p>		

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- $\gamma$ ) polypeptide, wherein said polynucleotide comprises a nucleotide sequence selected from the group consisting of:
  - (a) a nucleotide sequence encoding amino acid residues -25 to 149 of SEQ ID NO:2;
  - (b) a nucleotide sequence encoding the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
  - (c) a nucleotide sequence encoding amino acid residues 1 to 149 of SEQ ID NO:2;
  - (d) a nucleotide sequence encoding the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
  - (e) a homologue or analogue of any one of (a) to (d), wherein said homologue or analogue is at least 70% identical to any one of (a) to (d) and encodes a peptide or polypeptide having TNF- $\gamma$  activity;
  - (f) a fragment of any one of (a) to (d), wherein said fragment comprises at least 30 contiguous nucleotides in length derived from any one of (a) to (d);
  - (h) a nucleotide sequence of at least 30 nucleotides in length that is capable of hybridizing to any one of (a) to (e) wherein said nucleotide sequence encodes TNF- $\gamma$  or is derived from a nucleotide sequence that encodes TNF- $\gamma$ ; and
  - (i) a nucleotide sequence complementary to any one of (a) to (h).
2. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes amino acid residues -25 to 149 of SEQ ID NO:2.
3. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes amino acid residues 1 to 149 of SEQ ID NO:2;
4. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit



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No. 75927.

5. The isolated polynucleotide of claim 1 wherein said nucleotide sequence encodes the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.

6. The isolated polynucleotide of claim 1 wherein the percentage identity to a homologue or analogue of any one of (a) to (d) is at least 95%.

7. The isolated polynucleotide of claim 1 wherein the fragment of any one of (a) to (d) comprises at least 50 contiguous nucleotides in length derived from any one of (a) to (d).

8. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- $\gamma$ ) polypeptide, wherein said polynucleotide comprises the nucleotide sequence set forth as SEQ ID NO:1 or at least 30 contiguous nucleotide residues derived therefrom.

9. An isolated polynucleotide which encodes a tumor necrosis factor (TNF- $\gamma$ ) polypeptide, wherein said polynucleotide comprises a nucleotide sequence which is identical to the nucleotide sequence of the human cDNA contained in ATCC Deposit No. 75927 or at least 30 contiguous nucleotide residues derived therefrom.

10. An isolated polynucleotide that comprises a nucleotide sequence that is complementary to the nucleotide sequence of the isolated polynucleotide according to claim 8.

11. An isolated polynucleotide that comprises a nucleotide sequence that is complementary to the nucleotide sequence of the isolated polynucleotide according to claim 9.



12. The isolated polynucleotide according to any one of claims 1 to 11 comprising DNA.
13. The isolated polynucleotide of claim 12 wherein the DNA is genomic DNA.
14. A vector comprising the isolated polynucleotide according to any one of claims 1 to 13.
15. A host cell transformed or transfected with the polynucleotide according to any one of claims 1 to 13 or the vector of claim 14.
16. The isolated polynucleotide according to any one of claims 1 to 13 in operable connection with a heterologous regulatory sequence which controls gene expression.
17. A method of producing a polynucleotide which encodes TNF- $\gamma$  comprising hybridizing at least 30 contiguous nucleotides derived from SEQ ID NO:1 under stringent hybridization conditions with nucleic acid for a time and under conditions sufficient for hybridization to occur and then detecting said hybridization.
18. A method of producing a tumor necrosis factor (TNF- $\gamma$ ) polypeptide, said method comprising incubating or growing the host cell of claim 15 for a time and under conditions sufficient for expression of the polypeptide encoded by the introduced polynucleotide in said cell to occur.
19. A method of producing a cell capable of expressing a a tumor necrosis factor (TNF- $\gamma$ ) polypeptide, said method comprising transforming or transfecting a cell with the vector of claim 14.
20. A recombinant tumor necrosis factor (TNF- $\gamma$ ) polypeptide when produced by the method of claim 18.



21. An isolated or recombinant tumor necrosis factor (TNF- $\gamma$ ) polypeptide which comprises an amino acid sequence selected from the group consisting of:
- (a) amino acid sequence shown as residues -25 to 149 of SEQ ID NO:2;
  - (b) amino acid residues 1 to 149 of SEQ ID NO:2;
  - (c) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
  - (d) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927;
  - (e) the amino acid sequence of an analogue or derivative of any one of (a) to (d) wherein said analogue or derivative is at least 70% identical to any one of (a) to (d) and has tumor necrosis factor (TNF- $\gamma$ ) activity; and
  - (f) a fragment of any one of (a) to (d) that is encoded by at least 30 contiguous nucleotide residues present in SEQ ID NO:1 or the human cDNA contained in ATCC Deposit No. 75927 or a degenerate nucleotide sequence thereto.
22. The isolated or recombinant polypeptide of claim 21 comprising amino acid residues -25 to 149 of SEQ ID NO:2.
23. The isolated or recombinant polypeptide of claim 21 comprising amino acid residues 1 to 149 of SEQ ID NO:2.
24. The isolated or recombinant polypeptide of claim 21 comprising the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.
25. The isolated or recombinant polypeptide of claim 21 comprising the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 75927.
26. An antibody which binds specifically to the isolated or recombinant

polypeptide according to any one of claims 20 to 25.

27. A compound which antagonises the activity of the polypeptide according to any one of claims 20 to 25 or a naturally-occurring form of said polypeptide, wherein said compound was not known previously to antagonise the activity of said polypeptide.

28. A compound which agonises the activity of the polypeptide according to any one of claims 20 to 25 or a naturally-occurring form of said polypeptide, wherein said compound was not known previously to agonise the activity of said polypeptide.

29. A method of treatment of a patient having need of human TNF- $\gamma$  comprising administering to the patient a therapeutically effective amount of the polypeptide according to any one of claims 20 to 25 or the compound of claim 28 or a composition comprising said polypeptide or said compound.

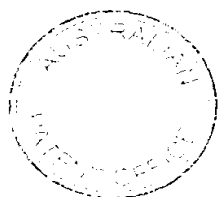
30. A method of treatment of a patient having need to inhibit human TNF- $\gamma$  comprising administering to the patient a therapeutically effective amount of the compound according to claim 27 or a composition comprising said compound.

31. A pharmaceutical composition comprising the polypeptide according to any one of claims 20 to 25 in combination with a pharmaceutically acceptable carrier.

32. The method of claim 29 wherein the polypeptide according to any one of claims 20 to 25 or the composition comprising said polypeptide is administered by providing to the patient DNA encoding said polypeptide and expressing said polypeptide *in vivo*.

33. A method of identifying a modulator of human TNF- $\gamma$  activity comprising:

(a) combining endothelial cells, Con A, [ $^3$ H]thymidine, and a compound to be tested for modulatory activity with the isolated or recombinant polypeptide according







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39. The method according to claim 38 wherein the mutation is determined by comparing the nucleotide sequence of the subject which encodes TNF- $\gamma$  with the nucleotide sequence of the nucleotide according to any one of claims 1 to 13, and wherein a difference between said nucleotide sequences is indicative of the mutation.

40. The method according to claim 38 or 39 when used to diagnose a tumor or a susceptibility to a tumor in a subject.

41. A method of diagnosing TNF- $\gamma$  expression in a subject comprising analysing a sample derived from said subject for the presence of the polypeptide according to any one of claims 20 to 25.

42. The method according to claim 41 comprising contacting a biological sample derived from said subject with an antibody molecule capable of binding to the isolated or recombinant polypeptide according to any one of claims 20 to 25 for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting said complex formed.

43. A method of inhibiting tumor cell growth in a subject comprising administering to the subject a therapeutically effective amount of the polypeptide according to any one of claims 20 to 25 or the pharmaceutical composition according to claim 31 for a time and under conditions sufficient for tumor growth to be inhibited.

44. Use of the polypeptide according to any one of claims 20 to 25 in the manufacture of a medicament to inhibit tumor cell growth , induce cell adhesion or promote endothelial cell growth in a human or animal subject.

45. Use of the isolated polynucleotide according to any one of claims 1 to 13 or the vector of claim 14 in the manufacture of a medicament to inhibit tumor cell growth , induce cell adhesion or promote endothelial cell growth in a human or animal subject.



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46. The vector of claim 14 substantially as hereinbefore described with reference to the Figures and/or Examples.

47. The host cell of claim 15 substantially as hereinbefore described with reference to the Figures and/or Examples.

48. The method according to claim 18 substantially as hereinbefore described with reference to the Figures and/or Examples.

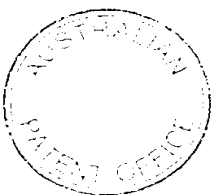
49. The method according to claim 19 substantially as hereinbefore described with reference to the Figures and/or Examples.

DATED this TWENTY FOURTH day of JUNE, 1999

**Human Genome Sciences, Inc.**

by DAVIES COLLISON CAVE

Patent Attorneys for the Applicants



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*Patents Act 1990*

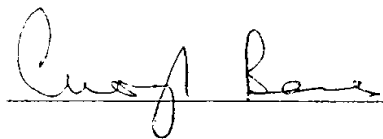
IN THE MATTER OF Australian Patent  
Application Serial No. 696764 by Human  
Genome Sciences, Inc.

-and-

IN THE MATTER OF Opposition thereto by  
Ludwig Institute for Cancer Research

THIS IS Exhibit PAWR-4  
referred to in the Statutory Declaration  
of Peter Adrian Walton Rogers  
made before me

DATED this 12<sup>th</sup> Day of November, 2001

A handwritten signature in cursive script, appearing to read "Craig Lane", written over a horizontal line.

(Signature of Witness)

Medical Practitioner